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# Coincidental Occurrence of Pernicious Anemia and Mycosis Fungoides in Two Elderly Males

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**We experienced two rare cases of pernicious anemia that presented in the course of mycosis fungoides in elderly males. Pernicious anemia has recently been reported to be caused by autoimmune gastritis that produces autoantibodies to gastric parietal cells and intrinsic factor. Immunological abnormalities in mycosis fungoides are reported to induce autoimmune diseases (i.e., autoimmune hemolytic anemia, anti-phospholipid antibody syndrome, arthritis, myasthenia gravis, necrotizing vasculitis, and vitiligo); the pernicious anemia in our two patients may have been closely related to the mycosis fungoides. Am. J. Hematol. 58:127–129, 1998.** © 1998 Wiley-Liss, Inc.

**Key words: mycosis fungoides; pernicious anemia; autoimmune disease; lymphoma**

## INTRODUCTION

Mycosis fungoides is a cutaneous T-cell lymphoma with helper phenotype [1,2]. Cutaneous T-cell lymphomas are sometimes accompanied by autoimmune diseases (i.e., autoimmune hemolytic anemia [3], anti-phospholipid antibody syndrome [4], arthritis [5], myasthenia gravis [6], necrotizing vasculitis [7], and vitiligo [8]). We encountered two cases of pernicious anemia that presented in the course of mycosis fungoides. Recent studies report that the major molecular targets recognized by the parietal cell autoantibodies are the α and β subunits of the gastric $H^+$, $K^+$ATPase (gastric proton pump) [9]. We discuss here the relationship between pernicious anemia and mycosis fungoides.

## CASE REPORTS

### Case 1

In March 1992, a 75-year-old male was admitted to our hospital with a 1-year history of developing scaly plaques of the skin that had initiated from the right hip. He had no previous history of exposure to mutagens or carcinogens. The plaques involved more than 10% of the body surface. Physical examination revealed left axillar lymphadenopathy. There was no icterus, anemia, or hepatosplenomegaly. Computed tomography (CT) of the abdomen revealed no evidence of lymph node swelling. Histological examination of the skin revealed mild hyperkeratosis and a band infiltrated with atypical lymphocytes. Electron microscopic examination of the skin revealed Pautrier's microabscesses. Lymph node biopsy was not performed. The laboratory findings were: Hb 12.8 g/dl; MCV 108.5 fl; platelet 19.1 × $10^9$/L; WBC 8.1 × $10^9$/L; LDH 398 IU/L (normal 230–420 IU/L); and HTLV-1 (−). The peripheral blood showed no Sèzary cells. He was diagnosed as having mycosis fungoides, clinical, stage IIA, and treated with photochemotherapy (PUVA). He was discharged in June 1992, and treatment was maintained with intermittent PUVA.

In May 1994, the patient gradually complained of shortness of breath. He was readmitted because of general fatigue in June 1994. Physical examination revealed severe anemia, atrophy of the tongue papillae, hepatomegaly, and skin eruptions on both legs. No lymphadenopathy or splenomegaly was detected. Results of neurological examination were normal. The laboratory findings were: Hb 6.8 g/dl; RBC 1.89 × $10^{12}$/L; Ht 20.1%;

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MCV 106.4 fl; MCH 36.3 μg; MCHC 33.0 pg; platelet $12.5 \times 10^9$/L; and WBC $4.2 \times 10^9$/L; the reticulocyte count was $28 \times 10^3/\mu l$. Hypersegmented neutrophils were found in the peripheral blood. The bone marrow showed marked hypercellularity and megaloblasts. Cytogenetic analysis revealed normal karyotypes. The serum levels of GOT, GPT, LDH, T-Bil, Fe, UIBC, and ferritin were 23 IU /L (normal 10–27 IU/L), 16 IU/L (normal 6–34 IU/L), 1,019 IU/L (normal 230–420 IU/L), 0.9 g/dl (normal 0.1–0.4 mg/dl), 159 μg/dl (normal 94–178 μg/dl), 21 μg/dl (normal 120–250 μg/dl), and 580 ng/ml (normal 40.7–335.8 ng/dl), respectively. The serum vitamin B12 level was less than 30 pg/ml (normal 230–800 pg/ml), but the serum folate level was normal. Autoantibodies to parietal cells and intrinsic factor were positive. The result of a microsome test was ×1,600 and that of a thyroid test was ×100. The serum levels of TSH, free T3, and free T4 were 2.2 μU/ml (normal 0.5–5.5 μU/ml), 2.9 pg/ml (normal 2.4–4.5 pg/ml), and 1.0 ng/dl (normal 0.81–2.13 ng/dl), respectively.

Lymphocyte subpopulations (CD3, CD4, CD8, CD19, CD20, CD16, CD56, and CD57), NK cell activity, and ADCC activity were normal. The serum levels of IgG, IgA, IgM, IgD, and IgE were 1,623 mg/dl (normal 770–1,700 mg/dl), 366 mg/dl (normal 90–450 mg/dl), 79 mg/dl (normal 60–250 mg/dl), 2.3 mg/dl (normal 0–12.3 mg/dl), and 199.1 IU/ml (normal 0–500 IU/ml), respectively. He was diagnosed as having pernicious anemia and was treated with hydroxocobalamin. His symptoms subsided and he was followed as an outpatient.

### Case 2

In December 1991, a 65-year-old male was admitted to our hospital because of systemic erythematous eruptions. He had no previous history of exposure to mutagens or carcinogens. He was diagnosed as having mycosis fungoides, clinical stage IIA by skin biopsy. The laboratory data results were: Hb 15.0 g/dl; RBC $4.64 \times 10^{12}$/L; Ht 48.5%; MCV 104.6 fl; MCH 32.3 μg; MCHC 30.9 pg; WBC $7.3 \times 10^9$/L; Plt $24.9 \times 10^9$/L; LDH 366 IU/L; and HTLV-I (−). He recovered after treatment with PUVA and glucocorticoid, and his condition was maintained with the same therapy.

In March 1994, the patient exhibited slight anemia on medical examination. In June 1994, he was referred to our hospital for evaluation of the anemia. Hepatomegaly on physical examination was detected. No splenomegaly or lymphadenopathy was found. Neurological findings were normal. The laboratory findings were: Hb 10.6 g/dl; RBC $2.62 \times 10^{12}$/L; Ht 30.8%; MCV 117.7 fl; MCH 40.4 μg; MCHC 34.4 pg; platelet $20.5 \times 10^9$/L; and WBC $4.9 \times 10^9$/L; the reticulocyte count was $33 \times 10^3/\mu l$. Hypersegmented neutrophils were found in the peripheral blood, and the bone marrow showed marked hypercellularity and megaloblasts. Cytogenetic analysis revealed normal karyotypes. The serum levels of GOT, GPT, LDH, T-Bil, Fe, UIBC, and ferritin were 24 IU/L, 16 IU/L, 550 IU/L, 1.1 mg/dl, 85 μg/dl, 192 μg/dl, and 173.6 ng/ml, respectively. The serum vitamin B12 level was 62 pg/ml, but the serum folate level was normal. Autoantibodies to parietal cells and intrinsic factor were positive. The result of a microsome test was ×102,400 and that of a thyroid test was ×25,600. The serum levels of TSH, free T3, and free T4 were 2.9 μU/ml, 3.7 pg/ml, and 1.2 ng/dl, respectively. Lymphocyte subpopulations (CD3, CD4, CD8, CD16, CD56, and CD57) and NK cell activity were normal. He was diagnosed as having pernicious anemia and treated with hydroxocobalamin. His symptoms subsided and he was followed as an outpatient.

## DISCUSSION

Primary cutaneous lymphoma is classified as either cutaneous T-cell lymphoma or cutaneous B-cell lymphoma [10]. Mycosis fungoides is a cutaneous T-cell lymphoma with a helper phenotype [1,2]. The pathological entities of cutaneous T-cell lymphoma involve mycosis fungoides, Sèzary's syndrome, pleomorphic T-cell lymphoma, and anaplastic large cell lymphoma [11]. The initial clinical manifestation of cutaneous T-cell lymphoma is cutaneous infiltration, and the diagnosis is usually established by skin biopsy [12]. Peripheral blood involvement is closely correlated with the severity of skin lesions, advanced stage, and poor prognosis [13]. Though peripheral blood involvement may be subtle in mycosis fungoides, it is prominent in Sèzary's syndrome.

Pernicious anemia was reported to be caused by autoimmune gastritis that produces autoantibodies to gastric parietal cells and intrinsic factor [14]. It is reported that the major molecular targets recognized by the parietal cell autoantibodies are the α and β subunits of the gastric $H^+$, $K^+$ATPase (gastric proton pump) [9]. Other autoantibodies are also found in pernicious anemia (anti-thyroid antibody 55%, anti-nuclear antibody 11%) [15]. Therefore, pernicious anemia is also recognized as an autoimmune disease and is currently termed an organ-specific autoimmune disease.

B cell lymphomas are accompanied by various autoimmune diseases, i.e., systemic lupus erythematosus [16], Sjögren's syndrome, and rheumatoid arthritis [17]. Autoimmune hemolytic anemia (AIHA) [18] and antiphospholipid antibody syndrome [19] are seen accompanied by B-cell lymphomas. Although many studies suggest that lymphoma cells do not produce autoantibodies [20], recent studies have revealed that B-cell lymphoma cells are directly committed to the production of autoantibodies [21]. It has been reported that antibodies of the IgM class produced by CD5 positive-B cells in lymphoid malignancy are multispecific autoantibodies [19]. Re-

cently, not only CD5-positive B-cells of chronic lymphocytic leukemia [20] but also CD5-negative B-cells of B-cells lymphoma have been found to be committed to the production of autoantibodies [21].

In contrast, T-cell lymphomas are rarely accompanied by autoimmune diseases. In a few reports, peripheral T-cell lymphomas, pleomorphic T-cell lymphoma, and cutaneous T-cell lymphoma have been accompanied by autoimmune diseases [3–8,22–24]. We suspect that vitamin $B_{12}$ malabsorption had already started when mycosis fungoides occurred in these 2 patients, because Case 1 had mild macrocytic anemia from the start and Case 2 had a high MCV when first seen, and postgastrectomy megaloblastic anemia exhibits symptoms about 5 years after total gastrectomy. Therefore, pernicious anemia may be accompanied by mycosis fungoides or may precede it. It is reported that some autoimmune diseases, especially organ-specific autoimmune diseases, tend to involve neoplasm complications [15]. Recent work indicates that the risk of developing a neoplasm (e.g., cancer of the stomach, esophagus, pancreas, myeloid leukemia, lymphoma, or multiple myeloma) was significantly higher in persons with pernicious anemia than in the general population [25]. The possibility that the immunological aberrations in pernicious anemia cause mycosis fungoides cannot be excluded.

In conclusion, the pernicious anemia in our two cases may have been closely related to their mycosis fungoides.

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